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Therapy Assessment: The Needs and Opportunities of Imaging as Bio- or Surrogate Markers - A Strategic Perspective

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Abstract: Imaging procedures are used as biomarkers in drug development in a variety of ways. Imaging frequently determines patient eligibility for trials, by indicating presence, location and/or stage of disease. Phenotypic information from imaging studies is used to enrich clinical trial populations with subjects most likely to benefit from the targeted therapy under study, thereby potentially reducing the number of subjects that need to be studied. The FDA accepts time-to-progression (TTP) as an outcome measure for approval of many oncologic drugs and imaging is the major component or indicator of response rate or TTP in cancer trials. Tumor shrinkage is the most commonly used imaging surrogate marker at present, but functional imaging tests such as FDG-PET, DCE-MRI, MR spectroscopy and optical techniques have shown promise in clinical trials and are undergoing more rigorous validation.

Although several new oncology drugs have reached the market over the past few years, more than 80% of drugs for all indications entering clinical development do not get marketing approval, with many failing late in development often in Phase III trials, because of unexpected safety issues or difficulty determining efficacy, including confounded outcomes. These factors contribute to the high costs of oncology drug development and clearly show the need for faster, more cost-effective strategies for evaluating oncology drugs and better definition of patients who will benefit from treatment. Similar issues and concerns exist for diseases other than cancer. Remarkable advances in the understanding of neoplastic progression at the cellular and molecular levels have spurred the discovery of molecularly-targeted drugs. This progress along with advances in imaging and bioassay technologies are the basis for describing and evaluating new biomarker endpoints as well as for defining other biomarkers for identifying patient populations, potential toxicity, and providing evidence of drug effect and efficacy.

In oncology, the gold standard clinical trial endpoint is overall survival, which may require long term studies and may be confounded by deaths from causes other than the patient's cancer. Over the years, the oncology community and the FDA in evaluating oncologic therapies have come to rely on other endpoints that from a scientific perspective are regarded as correlates of clinical benefit. These endpoints are objective response (OR), time to progression (TTP), disease-free survival (DFS) and progression free survival (PFS). All are determined by biomarkers measuring the cancer's extent. Anatomic imaging using one- or two-dimensional measurements to characterize cancers has been used traditionally to make these measurements in all aspects of cancer patient management from diagnosis and staging to monitoring response to therapy and disease progression.

However, the measurements made using standard anatomic imaging techniques are often inadequate for characterizing the cancer, especially for monitoring the effects of drugs that do not cause tumor

shrinkage or for cancers that progress slowly or metastasize diffusely. Newer imaging modalities including volumetric and functional imaging show high promise as the basis for characterizing better biomarkers of cancer. For example, clinical trials in breast cancer and other settings (*e.g.*, non-small cell lung cancer (NSCLC) and esophageal cancer) have demonstrated that 2-[^{18}F]-fluoro-2-deoxyglucose positron emission tomography (FDG-PET), a functional imaging modality, can provide an early indication of therapeutic response that is well-correlated with clinical outcome. FDG-PET thus has the potential to improve patient management, particularly by signaling the need for early therapeutic changes in non-responders and partial responders, thereby obviating the side effects and costs of ineffective treatment. As an early surrogate for clinical benefit, the modality also has the potential to facilitate oncologic drug development by shortening Phase 2 trials and detecting clinical benefit earlier in Phase 3 investigations.

Similarly, newer laboratory techniques based on advances in understanding of cellular and molecular biology hold promise as robust biomarkers that directly reflect neoplastic progression. Many of these biomarkers are based on genomic, proteomic, or immunogenic assays. Other examples are tumor burden biomarkers, which are often modulated by drug intervention, but may not be on the causal pathway or directly implicated in mechanisms of neoplastic progression. They are cellular proteins associated with tumor appearance or progression, *e.g.*, carcinoembryonic antigen (CEA), α-fetoprotein (✂FP), prostate specific antigen (PSA), CA-125, or CA-19-9. Often these biomarkers are used to monitor the effects of chemotherapy or other treatment. These biomarkers are being evaluated alone and in combination with imaging modalities for determining efficacy and identifying patients suitable for treatment.

These issues highlight the need for faster, more efficient, and more cost-effective development of cancer therapeutics and for better definition of patients likely to benefit from treatment. As addressed by the recent Food and Drug Administration (FDA) Critical Path Initiative, collaborative interactions among such scientific knowledge areas as bioinformatics, genomics, materials science, and imaging technologies are needed to design and implement better drug development tools. Important among these tools are functional molecular imaging methods that enable visualization of phenotypic expression of key targets in the cancer disease processes. Unlike anatomic imaging, functional imaging methods display biochemical and physiologic abnormalities underlying the cancer rather than the structural consequences of these abnormalities. Imaging-based biomarkers have many potential uses in all phases of the drug development process, from target discovery and validation to pivotal clinical trials for drug registration (see also ref. 15). First, as disease biomarkers, imaging end points can be employed to define, stratify, and enrich study groups. One such approach is to apply imaging-based methods to identify appropriate patient populations in which to test targeted agents. Second, some clinical imaging methods (e.g., DCE MRI) have potential to facilitate early clinical pharmacokinetic/pharmacodynamic assessments, particularly in patients where traditionally there are no direct measures of pharmacokinetics/pharmacodynamics throughout the tissues of the body and at the target. These approaches could be used in early studies comparing lead candidates designed to interact with the same target. A third area where imaging-based biomarkers have promise for speeding drug evaluation is by replacing or supplementing time- and labor-intensive dissection and histologic analyses in both preclinical and clinical testing. These noninvasive approaches may enable longitudinal preclinical studies with greater relevance to future clinical study designs. Finally, as biomarkers of tumor response, imaging end points can also serve as early surrogates of therapy success.

Magnetic resonance imaging has served in clinical cancer detection, diagnosis, and intervention and has been employed in the development of drug therapies. Two MR methods in particular, dynamic contrast enhancement MRI (DCE-MRI) and magnetic resonance spectroscopy (MRS), have shown significant potential to produce rapid, accurate, *in vivo* assessment. In recent years, their use in drug trials has been increasing, despite the fact that issues such as standardization and reliability have

limited their broad use. MRI and MRS can be important tools in new-drug development, especially to demonstrate biological activity and evaluate pharmacokinetic-pharmacodynamic relationships in early phase trials. One example of the use of MRI in drug development is the measurement of the exposure-dependent effects of drugs targeting the tumor vasculature (e.g., anti-angiogenesis) occurring prior to tumor shrinkage (1, 2). MRI and MRS have been used to monitor total choline levels as a marker in functional imaging for adjuvant therapy for cancer, providing information about therapeutic effects within days after treatment (3). Future applications may detect other molecules or reveal changes in metastatic sites. Ultimately, MRI and MRS could contribute significantly to predicting patient response to therapy and enhance survival.

Challenges to the development and implementation of imaging modalities in drug development include the lack of validation and standardization of new as well as established imaging methods. The identification and evaluation of biomarkers require access to and systematic analysis of large amounts of data, new technologies and extensive research resources. Further, there is a requirement for convergence of research, regulatory and drug developer thinking—an effort that will not be accomplished by individual scientists or research institutions. To this end, NCI, FDA, academic researchers and industry have entered into collaborations to identify biomarkers that will provide clearer pictures of a patient's cancer and its response to therapy in a timely fashion. The NCI and FDA are developing a strategic plan for evaluation of biomarkers to address these needs for collaborative research to identify the best biomarkers for oncology, to standardize data collection and analysis, and to provide a pathway for establishing the use of new biomarker tools in oncology drug development and patient care. This plan includes public-private partnerships with the pharmaceutical and imaging device companies.

Working groups composed of subject-matter experts are being formed to:

- Select the imaging modalities and clinical settings that will provide the best possible opportunities for development of biomarkers useful in oncologic drug development
- Priority rank biomarkers for testing
- Create research and business plans for development of each biomarker, including:
    - Definition of the biomarker (*i.e.*, what will be measured and calculated);
    - Instruments or reagents to be used,
    - Standardized acquisition parameters for imaging, bioassay and tissue data;
    - Clinical studies performed to validate the biomarker assay (including development and analyses of retrospective databases) and to evaluate the biomarker as a correlate of clinical status;
    - Further data and analyses required to bring the biomarker to routine use in clinical trials, and publication of methods and results (including guidance from the FDA).

To begin the process of developing consensus on standards for performing the imaging studies, NCI convened 2 workshops in the past year, one for MR and one for FDG-PET. The recommendations from the MR workshop are available on the NCI CIP website (imaging.cancer.gov) and will be published in greater detail in magnetic resonance literature in the near future. Building on the recommendations of earlier workshops on this topic (1), the MR workshop attendees developed consensus recommendations for MR measurement methods at 1.5-Tesla and endpoints for use in Phase 1/2a trials of anti-cancer therapeutics affecting tumor vascular function. Specific recommendations were made for the type of measurement, images to be acquired prior to contrast injection, requirements for contrast agent injection, the dynamic acquisition protocol, primary endpoints, measurement requirements for the primary endpoints, secondary endpoints, trial design, nomenclature, image analysis, data reduction, and the region of interest. Although these should provide guidelines for the use of DCE-MRI in drug development, it was recognized that the potential applications are much broader and a need for considerable research in this area remains. There is a need to evaluate the relationship of DCE-MRI measurements to clinical response (both pre-treatment and early after treatment). The attendees suggested an initial evaluation in colorectal

cancer and renal cell cancer. The need to explore DCE-MRI at 3 Tesla was noted, together with the need to compare 3 T results with 1.5 T results in settings with established vascular effects. New macromolecular contrast agents should be explored as they become available. The workshop attendees suggested that public domain analysis software should be made available and/or standard analysis capabilities built into MR systems. Other data analysis related issues requiring further exploration include the following: automation, normalization function (e.g., blood, muscle, spleen), impact of ROI definition on variability, consensus on acceptable statistical measures of reproducibility and information content of alternate (both simple and complex) analysis approaches. It was noted that data sets with known outcome available in a public database and an improved T_1 phantom could help evaluate analysis methods. Technical improvements that could be implanted to substantially improve the performance of DCE-MRI include parallel imaging, motion robustness (e.g., navigator echoes), robust registration algorithms, pulse sequences providing greater coverage, and quantitative pulse sequences. It was noted that a 'standard' tissue (e.g., benign prostatic hyperplasia, meningioma) might be useful to evaluate method variability independent of biological variability.

With a goal of standardizing the application of MRS, the workshop members agreed to focus on prostate, brain, and breast cancers. Multi-site trials with a single protocol must be conducted to verify the MRS techniques. For this to occur, certain issues must be resolved, including the use of many vendors, models, and methodologies. In fact, researchers possibly must bring MRS to a higher level of maturity before using it in multi-center trials. This would include development of quality assurance criteria. Researchers need to develop resources, such as links with industry, define metrics and software to produce data, and interface with industry regarding them. Metric standards should be incorporated into the scanners.

References

1. Leach, MO, Brindle KM, Evelhoch JL, et al. The assessment of antiangiogenic and antivascular therapies in early-stage clinical trials using magnetic resonance imaging: issues and recommendations. Br J Cancer 2005;92:1599-610.

2. Morgan B, Thomas AL, Drevs J, et al. Dynamic contrast-enhanced magnetic resonance imaging as a biomarker for the pharmacological response of PTK787/ZK222584, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinases, in patients with advanced colorectal cancer and liver metastases. J Clin Oncol 2003;21(21):3955–64.

3. Meisamy S, Bolan PJ, Baker EH, et al. Predicting response to neoadjuvant chemotherapy of locally advanced breast cancer with in vivo 1H MRS: A pilot study at 4 Tesla. Radiology 2004;233:424–31.